**Citation:**

Wang C, Harris WS, Chung M, Lichtenstein AH, Balk EM, Kupelnick B, Jordan HS, Lau J. n-3 Fatty acids from fish or fish-oil supplements, but not alpha-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. *Am J Clin Nutr*. 2006 Jul;84(1):5-17.

**PubMed ID:** 16825676

**Study Design:**

Systematic Review

**Class:**

M - Click here for explanation of classification scheme.

**Research Design and Implementation Rating:**

POSITIVE: See Research Design and Implementation Criteria Checklist below.

**Research Purpose:**

To systematically review the literature on the effects of n-3 fatty acids on cardiovascular disease outcomes and adverse events.

**Inclusion Criteria:**

- English language studies
- Original data reported on the effect of any type of n-3 fatty acid (FA) intake in human adults on all-cause mortality and the following clinical cardiovascular disease (CVD) outcomes:
  - cardiac death
  - sudden death
  - myocardial infarction(MI)
  - stroke
- Primary prevention studies (general population without a history of CVD)
- Secondary prevention studies (patients with a history of CVD)
- Randomized controlled trials (RCTs)
- Prospective cohort studies that followed patients for ≥ 1 year
- Case control studies that reported intakes of n-3 FAs or fish
- For purpose of reviewing adverse events and drug interactions - prospective human trials of any duration or dosage

**Exclusion Criteria:**

- Supplementation with > 6 grams n-3 FAs/day (12-18 large capsules)
- Case-control and cohort studies based on n-3 FA biomarkers that did not include estimates of dietary intakes

**Description of Study Protocol:**

**Search procedure and terms:**

- Comprehensive search of medical literature from 1966 to July 2005 in:
  - MEDLINE
  - PreMEDLINE
  - EMBASE
  - Cochrane Central Register of Controlled Trials
  - Biological Abstracts
  - Commonwealth Agricultural Bureau of Health
- Domain experts consulted
- References of retrieved articles examined
- Search terms:
- the specific FAs,
- fish and other marine oils
- specific plant oils: flaxseed, linseed, rapeseed, canola, soy, walnut, mustard seed, butternut, and pumpkin seed

**Design:** Systematic review

**Blinding used (if applicable):** not applicable

**Intervention (if applicable):**

Grading methodologic quality of studies:

- Each study appraised using a 3-category summary quality grade
  - approach is applicable to each type of study design
- Categories:
  - grade A: results are valid without obvious major bias
  - grade B: study is susceptible to some bias that is unlikely to invalidate the results
  - grade C: significant bias is present that may invalidate the results

**Statistical Analysis**

Meta-analyses not performed because of the heterogeneity of study designs, background diets, endpoint definitions, and baseline fish or n-3 FA intakes.

**Data Collection Summary:**

**Timing of Measurements:** not applicable

**Dependent Variables**

- Cardiac death
- Sudden death
- Myocardial infarction
- Stroke
- Implantable cardioverter defibrillators (ICDs)

**Independent Variables**

- Fish consumption
- Dietary supplementation of n-3 FAs

**Data extracted:**

- Study design
- Population demographics
- Background diet
- Intervention or exposure
- CVD outcome
- Data:
    - RCTs: relative risks of CVD outcomes between n-3 FA intervention and controls
    - Prospective cohort studies: data on the estimates of fish or fish-oil consumption and the associated effect
    - Observational studies: n-3 FA intakes as quartiles or quintiles (quantiles) and odds or risk ratios for clinical outcome of interest (results were translated into a qualitative scale to faciltate interpretation and comparison across studies, accounting for use of different quantiles in studies)

**Control Variables**

**Description of Actual Data Sample:**

**Initial N:** 8039 abstracts; 842 full text articles; 395 clinical studies also reviewed for potentially relevant human data on adverse events

**Attrition (final N):** 46 articles identified on CVD outcomes

- 25 prospective cohort studies
- 7 case-control studies
- 14 RCTs

**Age:** not applicable

**Ethnicity:** not applicable

**Other relevant demographics**

**Anthropometrics**

**Location:** International studies

**Summary of Results:**

**Key Findings**

- Overall, the data from the secondary and primary prevention studies support the hypothesis that consumption of very-long-chain n-3 FAs from fish and fish-oil supplements reduces all-cause mortality, myocardial infarction, cardiac and sudden death, and stroke.
- Studies in patients with ICD found inconsistent antiarrhythmic effects and no significant

overall effect on mortality.
- Most secondary prevention trials (14 RCTs, 1 cohort study) reported that fish oil significantly reduced all-cause mortality, myocardial infarction, cardiac and sudden death or stroke.
- Primary prevention studies included 25 prospective cohort studies, 7 case-control studies, 1 RCT. Most cohort studies reported that fish consumption was associated with lower rates of all-cause mortality and adverse cardiac outcomes.
- Effects on stroke were inconsistent.
- No high-quality evidence supports a beneficial effect of ALA.

## Secondary prevention studies

- RCTs: n=11
    - total patients: N = 19,403
- prospective cohort study (n = 1)
    - total N = 415

***Supplement trials*** (n = 6 RCTs)

- Grade A or B quality: n=5
- EPA or EPA+ DHA supplements evaluated
    - dosages: 0.27 - 4.8 grams/day
- One Grade B quality trial (n=11,324 patients with recent MI, 3.5y of follow-up) reported that 0.85 g EPA + DPA/day compared with a usual case-control group significantly reduced the relative risk of all-cause mortality (21%), cardiac death (35%) and sudden death (45%). There was a non-significant increase in strokes.
- Two small trials reported nonsignificant beneficial trends on peripheral arterial disease (N=120, 0.27 g EPA/day, Grade A quality) and on cardiovascular disease outcomes (N=59, 4.8 grams/day EPA + DHA, Grade B quality). One trial ( N=223, half with history of MI, Grade A quality) reported a nonsignificant trend of fewer CVD events among patients who took 1.7 g fish oil/day.
- One trial reported no beneficial effects of n-3 FA supplementation. (N=300 patients with recent MI, 3.4 grams EPA + DHA/day vs. control, Grade B quality)

***Diet or dietary-advice trials***

- Grade C quality: 4/5 trials
- No firm conclusions regarding the effects of either ALA or the marine n-3 FA could be reached from these trials.
    - Two Grade C quality dietary advice trials:
        - One (N=2033 males, recent MI, 2 year follow-up) reported a beneficial effect of advice to increase intake of oily fish on all-cause mortality, cardiac death, and fatal MI.
        - The second trial (N-3114 patients with stable angina, 50% with history of MI, 3-9 years follow-up) reported a nonsignificant increase in risk of all-cause mortality and cardiac death, and a significant increase in the risk of sudden death (hazard ratio = 1.54), especially in a group subrandomly assigned to receive fish-oil capsules
    - ALA
        - One Grade B quality study (N=266) reported a nonsignificant increase in the risk of all-cause mortality, which was low in intervention (6.3 grams ALA/day) vs control (1.0 grams ALA/day)

- Two Grade C quality studies reported significant reductions or trends toward lower rates of all-cause mortality, cardiac and sudden death, or nonfatal MI.

***Cohort study***

- One study (N=415 patients with coronary artery disease, 5 years follow-up) reported a significant decrease in all-cause mortality (RR=0.37) in patients who consumed >57 grams fish/day.

***Patients with implantable cardioverter defibrillators***

- RCTs: 3
- 1 to 2 years duration
- In one Grade B quality study, there was no significant decrease in total mortality between those who received fish oil (1.8 grams/day for 2 years), but there was a shorter to to the first episode of ICD therapy for ventricular tachycardia or ventricular fibrillation (VT/VF) and an increase ( $P < 0.001$) in recurrent VT/VF events in the patients who received fish oil.
- In patients who received 2.6 grams/day fish oil for 12 months (compared to olive oil), there was a trend toward a prolonged time to first VT or VF or death from any cause (risk reduction of 28%; $P = 0.057$). There was no difference in overall deaths between groups. (N=402 patients, Grade B quality study)
- Study on Omega-3 Fatty Acids and Ventricular Arrhythmia (SOFA) (unpublished)
  - small beneficial effect in 546 patients with an ICD who randomly received 2 grams/day fish oil or sunflower oil for 12 months.
  - no significant difference in combined outcome of VT/VF or death from any cause
  - In subgroup of 324 patients with prior MI, nonsignificant trend in combined outcome of VT/VF or death from any cause in those who received fish oil compared with placebo

## Primary-prevention studies

- RCT: 1 trial
- Prospective cohort studies: 25
- Case-control studies: 7
- conducted in the United States, Europe, China, and Japan
- Most estimated fish or fish-oil intakes
- Only 3 estimated ALA intakes
- **RCT**
  - One RCT of n=3 FA supplementation (N=13,578,50-59 years), randomly assigned to receive 10 mL flaxseed oil (5.5 grams ALA/day) or sunflower seed oil (0.14 grams ALA/day) for 1 year. No significant cardiovascular benefit of ALA supplementation
- **Cohort studies**
  - involved > 340,000 participants in total
  - significant reductions reported after multivariate adjustment in one or more of the CVD outcomes of interest

***All-cause mortality***

- Studies evaluating *fish-oil intake*:
  - Three large prospective cohort studies (>53,000 participants) reported significant reductions in all-cause mortality
  - One cohort study (N=41,836 females free of heart disease at baseline), estimated

marine n-3 FA intake was not associated with total mortality
        - In secondary analysis, ALA intake was modestly inversely associated with total mortality after multivariate adjustment
- Studies evaluating *fish consumption:*
    - Eleven prospective cohort studies provided data
        - Eight reported no reduction in all-cause mortality
        - Three reported associations between increased fish consumption and reduced mortality (Physicians' Health study, large cohort study(N-63,000 men from China), subset of 5103 diabetic women in the Nurses' Health Study

***Cardiac death***

- Studies evaluating n-3 FA consumption:
    - Two prospective cohort studies
        - 6 year cohort study ( N=21,930 men who smoked: no association of cardiac death with either ALA or EPA + DPA intake
        - MRFIT: (N=12,866 men):
            - no association between ALA intake and risk of cardiac death
            - highest quintile of EPA + DHA intake was associated with a 40% lower risk
- Studies evaluating fish consumption:
    - 15 cohort studies
        - 4 showed a statistically significant reduction in fatal and total coronary heart disease with higher fish consumption
            - one study (N=3910 older subjects, 9.3 years of follow-up) found a statistically significant lower risk of total ischemic heart disease associated specifically with higher intakes of oily fish
        - 8 showed some protective benefit
        - 4 cohort studies showed no benefit

***Sudden death***

- Two prospective cohort studies and 1 case-control study
    - Physicians' Health Study (N=20,551 mean, 11 years follow-up): 50% lower relative risk even in participants who ate fish only 1 time/month (>0.3 grams/month n-3 FA)
    - Chicago Western Electric Study (N=1822 men 30 years follow-up) found an association between higher fish consumption and lower rates of sudden death
    - Case control study (N=827) reported a significant decrease in sudden death with increasing fish intake and fish-oil consumption

***Myocardial infarction***

- Studies evaluating fish oil consumption: 3 large cohort studies and 1 case-control study of 148,802 participants showed benefits of n-3 FA intake
    - Nurses' Health Study (N=84,688 females): higher EPA + DHA intakes associated with 31% lower risk in the highest compared with lowest quintile
    - Physicians' Health Study and Zutphen Elderly Study (N=667 elderly males free of CAD for 10 years) reported no reductions in risk of MI with increase intakes of EPA + DHA or fish
- Studies evaluating fish consumption:
    - 4/9 cohort studies and 1 case-control study showed a statistically significant reduction in CHD

- 3 cohort studies and 1 case-control study found no reduction in risk

***Stroke***

- 5 prospective cohort studies and 1 case-control study
- Studies evaluating fish oil intake:
  - Health Professionals Follow-Up Study (N=43,671 men free of CVD; 12 years follow-up): reported significant reduction in ischemic strokes at all fish-oil intakes above the lowest quintile
  - Nurses' Health Study: non-significant trend of decreased strokes with increasing fish oil intake
- Studies evaluating fish consumption:
  - 12 prospective cohort studies and 1 case-control study
    - 3 large cohort studies showed a statistically significant reduction in stroke, particularly ischemic stroke.
      - Health Professionals Follow-Up Study reported a significant reduction in ischemic strokes with any level of fish consumption
      - Hiroshima/Nagasaki Life Span Study (N=30,827): those in the highest tertile of fish consumption had a lower risk of death from stroke than those in the lowest tertile; no association with hemorrhagic stroke
      - Cardiovascular Health Study - increased consumption of tuna or other nonfried fish was associated with a decrease in total stroke and ischemic stroke; but increased consumption of fried fish and fish sandwiches was associated with an increased risk of stroke; no association with hemorrhagic stroke
    - 3 cohort studies and 1 case-control study found a nonsignificant trend of decreased strokes with increasing fish consumption
    - An additional 5 cohort studies found no evidence that fish consumption reduces risk of stroke

**Adverse events**

- 247/395 articles provided no information on adverse events
- 71/148 studies reported $\geq$ 1 adverse event
- categorization and reporting varied widely across studies
- common GI symptoms (nausea, vomiting, 'mild' to 'severe' gastrointestinal disturbance) occurred at rates of ~4% at dosages < 3 grams/day and increased to ~ 20% at a dosage of 4 grams/day
- Clinically significant bleeding episodes addressed in 9 studies (2612 patients)
  - 4/9: no bleeding in either arm
  - 6/9: no consistent association between n-3 FA dose and risk of bleeding
- ALA intake and prostate cancer risk
  - one meta-analysis reported a 70% increase in risk

**Author Conclusion:**

Evidence suggests that increased consumption of n-3 FAs from fish or fish-oil supplements, but not of ALA, reduces the rates of all-cause mortality, cardiac and sudden death, and possibly stroke. The evidence for the benefits of fish oil is stronger in secondary than in primary prevention settings. Adverse effects appear to be minor.

***Reviewer Comments:***

***Research Design and Implementation Criteria Checklist: Review Articles***

| **Relevance Questions** | | |
|---|---|---|
| 1. | Will the answer if true, have a direct bearing on the health of patients? | Yes |
| 2. | Is the outcome or topic something that patients/clients/population groups would care about? | Yes |
| 3. | Is the problem addressed in the review one that is relevant to nutrition or dietetics practice? | Yes |
| 4. | Will the information, if true, require a change in practice? | Yes |

| **Validity Questions** | | |
|---|---|---|
| 1. | Was the question for the review clearly focused and appropriate? | Yes |
| 2. | Was the search strategy used to locate relevant studies comprehensive? Were the databases searched and the search termsused described? | Yes |
| 3. | Were explicit methods used to select studies to include in the review? Were inclusion/exclusion criteria specified and appropriate? Were selection methods unbiased? | Yes |
| 4. | Was there an appraisal of the quality and validity of studies included in the review? Were appraisal methods specified, appropriate, and reproducible? | Yes |
| 5. | Were specific treatments/interventions/exposures described? Were treatments similar enough to be combined? | Yes |
| 6. | Was the outcome of interest clearly indicated? Were other potential harms and benefits considered? | Yes |
| 7. | Were processes for data abstraction, synthesis, and analysis described? Were they applied consistently across studies and groups? Was there appropriate use of qualitative and/or quantitative synthesis? Was variation in findings among studies analyzed? Were heterogeneity issued considered? If data from studies were aggregated for meta-analysis, was the procedure described? | Yes |
| 8. | Are the results clearly presented in narrative and/or quantitative terms? If summary statistics are used, are levels of significance and/or confidence intervals included? | Yes |
| 9. | Are conclusions supported by results with biases and limitations taken into consideration? Are limitations of the review identified and discussed? | Yes |
| 10. | Was bias due to the review's funding or sponsorship unlikely? | Yes |